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A POPULATION-BASED STUDY OF SURVIVAL AND CHILDBEARING AMONG FEMALE SUBJECTS WITH BIRTH DEFECTS AND THE RISK OF RECURRENCE IN THEIR CHILDREN

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ABSTRACT

Background and Methods Persons with birth defects are at high risk for death during the perinatal period and infancy. Less is known about the later survival or reproduction of such persons. We studied a cohort that comprised 8192 women and adolescent girls with registered birth defects and 451,241 women and adolescent girls with no birth defects, all of whom were born in Norway from 1967 through 1982. The rate of survival was determined through 1992, and the rate of childbearing was determined through October 1997. We also estimated the risk of birth defects in the children of these subjects.

Results Among the subjects with birth defects, 80 percent survived to 15 years of age, as compared with 98 percent of those with no birth defects. Among the surviving subjects, 53 percent of those with birth defects gave birth to at least one infant by the age of 30 years, as compared with 67 percent of those with no birth defects. The subjects with birth defects were one third less likely to give birth by the age of 30 than those with no birth defects. The children of the subjects with birth defects had a significantly higher risk of birth defects than the children of those with no birth defects (relative risk, 1.6; 95 percent confidence interval, 1.3 to 2.1). This increased risk was confined entirely to the specific defect carried by the mother, with the relative risk of recurrence varying from 5.5 to 82 according to the defect. In contrast, there was no increase in the risk of having an infant with a different type of defect.

Conclusions Women and girls with birth defects have decreased survival as compared with those with no birth defects, especially in the first years of life, and are less likely to have children. In addition, they have an increased risk of having children with the same defect. (N Engl J Med 1999;340:1057-62.)

BIRTH defects are likely to recur in families. This pattern probably reflects not only shared genetic factors but also shared environmental factors. Although some studies have documented an increased tendency of women with birth defects to have children with a similar defect,[1,2] few studies have assessed the risk of other (dissimilar) defects in the children of such women. We approached the issue of familial risk through the use of a population-based registry of nearly 500,000 female subjects followed from birth to adolescence and adulthood. We used data from this registry to determine how birth defects affect rates of survival and childbearing and to determine the risk of birth defects in the children of affected women. In particular, we focused on a child's risk of having the same defect as his or her mother and of having a dissimilar defect.

METHODS

Population-Based Generational Data

The study is based on data from the Medical Birth Registry of Norway, a population-based registry of all births in Norway since 1967 (about 1.7 million). Stillbirths at 16 weeks of gestation or later are also included in the registry. There were 459,433 live or stillborn female infants delivered in Norway from 1967 through 1982; the survivors were between the ages of 15 and 30 years in 1997. This cohort was followed for survival through 1992 (when the most recent linkage with mortality records was carried out) and for childbearing through October 1997. The birth cohort was divided into those with a registered birth defect (8192, or 1.8 percent) and those without such a defect.

Classification of Birth Defects

The Medical Birth Registry of Norway records birth defects that have been diagnosed at the time of delivery or during the

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initial hospitalization, which lasts a minimum of five days. In this study, categories of birth defects were defined on the basis of the three-digit codes of the *International Classification of Diseases, 8th Revision* (ICD-8), with minor modifications. Altogether, 24 categories of birth defects were used, as in a previous study.[3] Hip dislocations were excluded from the category of limb defects. A similar defect in a child was defined as a defect with the same ICD classification as the defect in the mother. A dissimilar defect was any other defect in the child.[3]

Statistical Analysis

The reference group was made up of the adolescent girls and women without birth defects. Differences in the rates of survival and childbearing between those with birth defects and those without birth defects were estimated with standard actuarial methods at six-month intervals.[4] Childbearing was calculated as a ratio by dividing the number of subjects with specific birth defects who had children by the number with no birth defects who had children (observed:expected). All analyses with respect to childbearing were based only on surviving women.

We compared the risk of birth defects in the children of the subjects with birth defects with the risk in the children of the subjects with no birth defects. The relative risk of recurrence was estimated by the odds ratio. The overall odds ratio (with the 95 percent confidence interval) for all categories of maternal defects was estimated with a Mantel–Haenszel approach. The expected number of birth defects among the children of the subjects with specific defects was based on the risk of birth defects among the children of the subjects without birth defects. The 95 percent confidence interval for the ratio of childbearing among survivors with birth defects to that among survivors without birth defects was calculated by Cox proportional-hazards analysis.[4] Confidence intervals for odds ratios were calculated with SPSS[4] and StatXact[5] software. Exact tests were used when appropriate. All tests were two-tailed.

TABLE 1. RATES OF SURVIVAL AND CHILDBEARING AMONG FEMALE SUBJECTS ACCORDING TO YEAR OF BIRTH.

YEAR OF BIRTH	SUBJECTS	AGE IN 1997	SURVIVAL*	CHILDBEARING†
	no.	yr	percent	
1967–1969	99,261	28–30	96.7	61.9
1970–1972	95,805	25–27	97.2	40.9
1973–1975	87,415	22–24	97.5	20.4
1976–1978	76,738	19–21	97.8	6.8
1979–1982	100,214	15–18	98.1	0.5
1967–1982	459,433	15–30	97.4	26.9

*Data on survival are through 1992.

†The rate of childbearing is expressed as the percentage of all surviving subjects who had delivered at least one child. Data are through 1997.

TABLE 2. AGE-SPECIFIC DEATH RATES.

YEAR OF DEATH	SUBJECTS WITH BIRTH DEFECTS	SUBJECTS WITH NO BIRTH DEFECTS	RELATIVE RISK
	per 1000		
Stillborn	69.0	10.6	6.5
1st yr	113.5	7.7	14.8
2nd yr	7.4	0.6	12.0
3rd–4th yr	5.8	0.8	6.9
5th–9th yr	4.6	1.2	4.0
10th–14th year	2.6	0.6	4.6
≥15th yr	3.2	1.3	2.5

RESULTS

Total Rates of Survival and Childbearing

Among 459,433 female infants born from 1967 through 1982, 447,613 (97.4 percent) survived, of whom 120,469 (26.9 percent) had at least one recorded pregnancy by the end of 1997 (Table 1). The mortality among those with birth defects was 15 times as high in the first year of life and 12 times as high in the second year as among those without birth defects (Table 2). The relative risk decreased with age but was still more than 4 among children 10 to 14 years of age.

Among women 28 to 30 years old, 62 percent had delivered a live or stillborn infant. There was a total of 187,544 births among all the subjects. The majority of the children were their mothers' firstborns (65 percent); only 6 percent were born to mothers who already had two or more children. Figure 1 shows the cumulative rates of survival and childbearing for the subjects with birth defects and those without birth defects. The women and girls with birth defects had lower rates of survival than those without birth defects (80 percent vs. 98 percent). The proportion of survivors who had ever given birth was lower for the subjects with birth defects at every age (53 percent vs. 67 percent by the age of 30 years) (Fig. 1). On the basis of the cumulative childbearing rates of the subjects at the age of 30 years, the ratio of childbearing among the survivors with birth defects to that among the survivors without birth defects was 0.7 (95 percent confidence interval, 0.7 to 0.8; $P<0.001$). Taking into account both their higher mortality rates and their lower rates of childbearing, the subjects with birth defects were, on average, only 0.6 times as likely to give birth by the age of 30 years as those with no birth defects ($P<0.001$).

Rates of Survival and Childbearing According to the Category of Birth Defect

The total survival rate for the subjects with each of the 24 categories of birth defects and the ratio of observed to expected childbearing are shown in Figure 2. In general, the categories of birth defects in which survival was poor were associated with a reduced probability of childbearing among the survivors. For all defects with a ratio of observed to expected births below 0.75, women with the defect were significantly less likely to bear children than

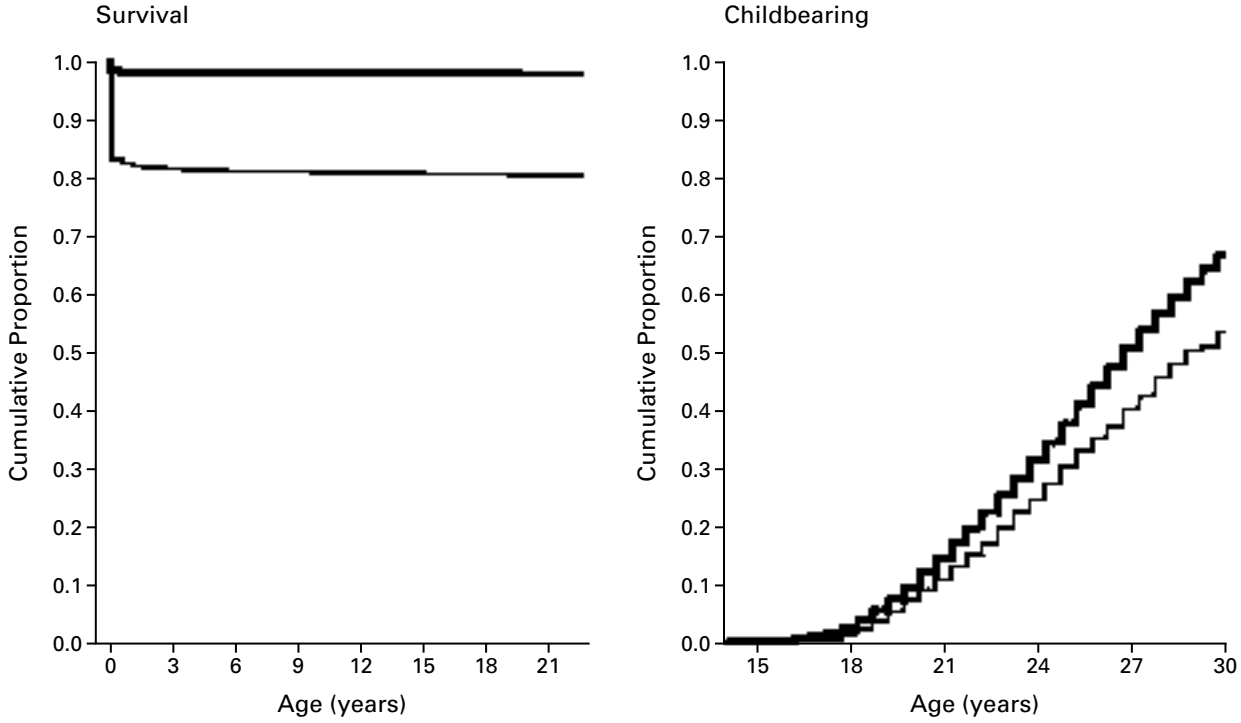

Figure 1. Cumulative Rates of Survival and Childbearing among Female Subjects Born with Birth Defects and among Those with No Defects.

The cohort has been followed through 1992 for survival and through 1997 for childbearing. Childbearing was calculated among survivors only. Thin lines represent data for the women with birth defects, and thick lines represent data for the women without birth defects.

women without the defect ($P<0.05$). For a few defects (e.g., Down's syndrome) the ratios were low despite high survival rates.

Birth Defects in the Second Generation

Of the 8192 subjects with birth defects, 1101 gave birth to a total of 1613 children. Sixty-two of these children (3.8 percent) had birth defects. The subjects with no birth defects had a total of 185,931 children, of whom 4418 (2.4 percent) had birth defects. Thus, the overall risk of birth defects was 1.6 times as high among the children of mothers who themselves had birth defects as among the other children (95 percent confidence interval, 1.3 to 2.1).

Contribution of Subjects with Birth Defects to the Total Risk of Birth Defects

Although the subjects with birth defects had a risk of bearing children with birth defects that was 1.6 times the risk among those without birth defects, these subjects constituted only about 1 percent of the women who gave birth. Thus, the higher risk among the subjects with birth defects accounted for only 5 of 1000 birth defects in the next generation (according to an estimate of population attributable risk[6]).

Similarity of Defects in Mothers and Children

Twenty-six subjects with birth defects had infants with the same defects, as compared with an expected number of 3.94 (Table 3). The types of maternal defects that recurred in the children were cleft palate, cleft lip, clubfoot, and limb defects. Among the children of the mothers with these birth defects as compared with the children of the mothers with no defects, the relative risks were as follows: cleft palate, 82; cleft lip, 38; clubfoot, 5.5; and limb defects, 5.6 ($P<0.001$, except for limb defects, in which $P=0.05$). In addition, 36 women with birth defects gave birth to children with dissimilar defects, as compared with an expected number of 34.6. The relative risk for each defect clustered near 1.0, with none being significantly different from 1.0 ($P>0.20$ for all defects). The pooled relative risk of a dissimilar defect was 1.0 (95 percent confidence interval, 0.7 to 1.4). Subjects with multiple defects could have complicated the evaluation of the recurrence of similar and dissimilar defects.[3] However, none of

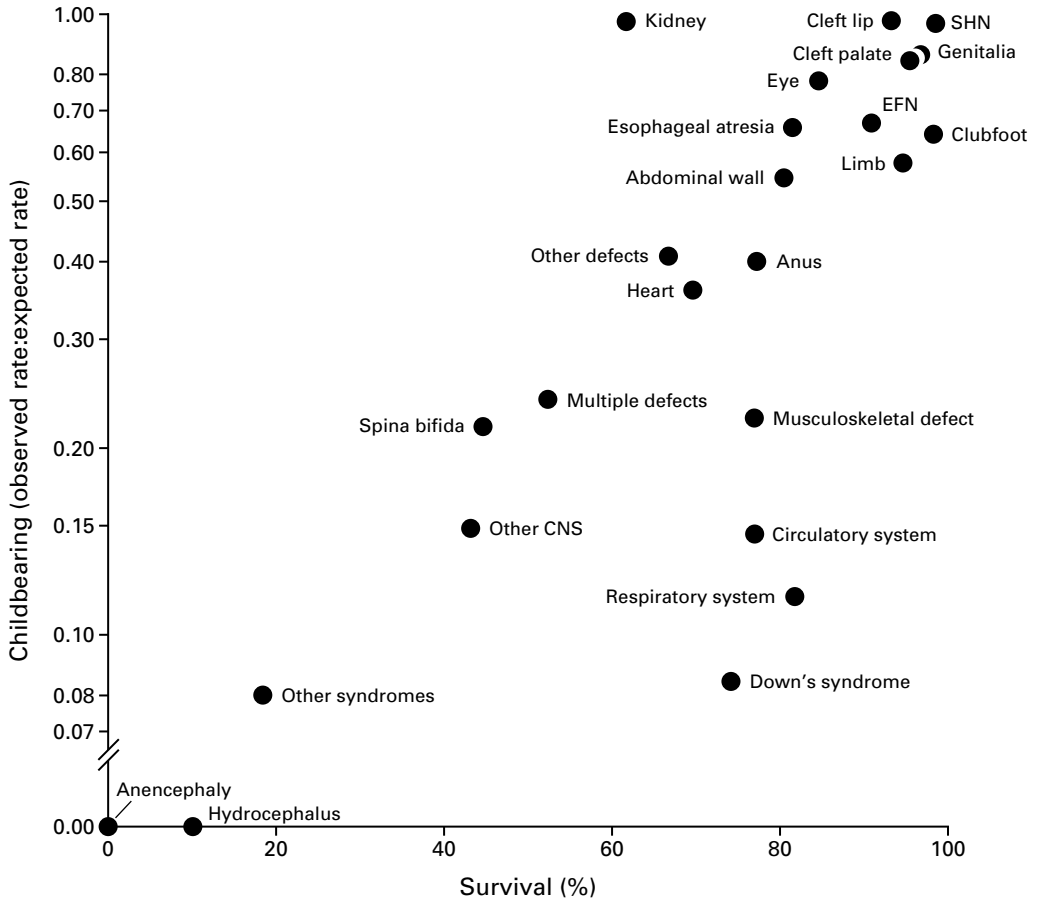

Figure 2. Rates of Survival and Childbearing among Female Subjects Born with Birth Defects According to Category of Defect. Childbearing was estimated as the ratio of the proportion of women with a specific type of birth defect who bore children to the proportion among women with no birth defects (observed:expected), and was calculated among survivors only. CNS denotes central nervous system; EFN ear, face, and neck; and SHN skin, hair, and nails.

the subjects with multiple defects had children with any defect.

DISCUSSION

Birth defects tend to recur in families. Genetic factors undoubtedly have a major role, with the expression of genetic risk further influenced by the probability of survival and eventual reproduction among girls and women with birth defects. There is seldom an opportunity in human populations to study these probabilities in a comprehensive fashion. Using a population registry of all births in Norway since 1967, we explored these issues in a cohort of nearly 500,000 female subjects followed from birth to adolescence and adulthood.

Many birth defects increase mortality in the first year of life.[7,8] A few defects (e.g., Down's syndrome) are associated with an increased risk of mortality throughout childhood.[8,9] In our study, nearly 20 percent of the original cohort with birth defects had died by the age of 15 years, as compared with 2 percent of those without birth defects. The high mortality among girls with birth defects before they reach reproductive age substantially reduces their potential genetic contribution to the next generation and selects against the evolutionary survival of alleles conferring an elevated risk of birth defects.

Women with birth defects who survive to reproductive age have a reduced likelihood of childbearing. This no doubt reflects social as well as biologic factors. The proportion of survivors who had children was lower for those with the types of birth defects associated with high mortality rates (Fig. 2). Thus, the birth defects that most often cause death may also cause more serious morbidity among the survivors. Some defects (e.g., anencephaly) are lethal and will therefore never recur, since the subject does not reproduce.

By the age of 30 years (the age of the oldest women in the cohort), the women with birth defects

TABLE 3. RISK OF SIMILAR AND DISSIMILAR BIRTH DEFECTS IN CHILDREN ACCORDING TO CATEGORY OF BIRTH DEFECT IN THE MOTHER.

DEFECT IN MOTHER*	NO. OF MOTHERS	NO. OF CHILDREN AT RISK	TOTAL NO. OF DEFECTS	SIMILAR DEFECT			DISSIMILAR DEFECT		
				NO. OF DEFECTS OBSERVED	NO. OF DEFECTS EXPECTED	ODDS RATIO (95% CI)†	NO. OF DEFECTS OBSERVED	NO. OF DEFECTS EXPECTED	ODDS RATIO (95% CI)†
Cardiac defect	54	75	3	0	0.13	—	3	1.7	1.8 (0.5–5.2)
Cleft palate	44	66	4	2	0.03	82 (13–290)	2	1.6	1.3 (0.2–4.4)
Cleft lip	104	149	11	7	0.20	38 (16–77)	4	3.4	1.2 (0.4–2.9)
Abdominal-wall defect	44	64	2	0	0.03	—	2	1.5	1.3 (0.2–4.6)
Clubfoot	453	666	32	15	2.80	5.5 (3.2–9.1)	17	13.1	1.3 (0.8–2.1)
Limb defect	159	236	7	2	0.37	5.6 (0.9–18.7)	5	5.3	0.9 (0.3–2.2)
All defects	1101	1613	62	26	3.94	6.8 (4.5–10.0)	36	34.6	1.0 (0.7–1.4)

*Defects are defined according to the *International Classification of Diseases, 8th Revision*. Not all categories of defects are listed, so numbers do not necessarily sum to totals shown.

†Mothers without the specific defect served as the reference group. CI denotes confidence interval.

were only 74 percent as likely to have given birth as the other women. Although it is too early to draw final conclusions about the lifetime fertility of women with birth defects, a continuation of this pattern would mean that such women are substantially less likely than other women to contribute offspring to the next generation. By the age of 30, the combined effects of higher mortality and reduced childbearing among Norwegian women with birth defects had lowered their overall contribution of offspring to the next generation by 40 percent.

Even women with birth defects associated with the highest survival had a reduced contribution to the next generation. All four types of defect that occurred in both the women and their children (cleft palate, cleft lip, clubfoot, and limb defects) were associated with relatively high survival, but the proportion of the women who ever gave birth among those with these defects was nonetheless 14 to 48 percent lower than that among the women with no defects.

For these reasons, a very small fraction of birth defects in the next generation is attributable to mothers with birth defects. In this cohort, the excess risk among the children of mothers with birth defects contributed about 0.5 percent of the birth defects in the next generation.

In family-based studies of birth defects, the focus typically is on a single type of defect.[2,10] Using a large population-based registry, we were able to include all types of defect. We found a moderately higher risk of any defect among the children of the subjects with birth defects than among the children of those without defects. However, this risk was confined to the particular defect carried by the mother. The risk carried across generations is likely to be mostly genetic. Environmental risk factors may also be shared by women and their children, but the intervening passage of years makes this less likely.

Few family studies have provided data on all birth defects in children. Carter et al.[1] reported on defects other than cleft lip in the children of probands with cleft lip, but they were unable to determine whether the risk was higher or lower than would be expected in the general population. Family studies typically lack the population data needed to estimate the relative risk of dissimilar defects. Among the children of the subjects with birth defects, we found no evidence of an increased risk of any type of defect other than the one carried by the mother. This was true for the subjects overall and for each type of maternal birth defect. This finding implies a degree of specificity in the genetic or other factors that are responsible for the risk of recurrence in children. It also offers some reassurance to affected women who may worry that their children will be susceptible to a variety of defects.

The Medical Birth Registry of Norway, like any registry based on routine medical birth records, does not contain data on all birth defects.[11] However, the infants of women with birth defects may be examined more carefully than the infants of women with no birth defects. The complete absence of an increase in dissimilar defects among the children of the subjects with birth defects, as compared with the rate in the children of the subjects without birth defects, suggests that increased ascertainment is not distorting our data.

Age or time trends in birth defects could distort observations in a cross-sectional cohort such as ours.

In general, the effects of maternal age on the risk of birth defects seem to be U-shaped, but limited.[12,13] The background rate of birth defects in the Medical Birth Registry has increased over time (from 2.1 percent in 1967 through 1982 to 2.5 percent in 1983 through 1997), most likely because of improved ascertainment. There are no trends related to age or time for the major defects that would affect the results of our study.

The Norwegian registry includes defects identified in the hospital during the first week after birth. The majority of all defects are detected at the time of birth. However, defects that are diagnosed later, such as cardiac defects, are less likely to be detected than those detected at birth (e.g., cleft lip or spina bifida). To the extent that defects diagnosed later are different from other defects, the picture provided by our data may not be complete. Moreover, given the composition of the cohort (comprising all female infants born from 1967 through 1982), only a small proportion has actually been followed to the age of 30 years. Caution must be used in making longitudinal interpretations of these cross-sectional data.

Our estimates of risk do not take into account the statistical interdependence of outcomes within the family structure. Although this factor may contribute unmeasured variability to some confidence intervals, it has probably had little effect on the risk estimates themselves. When we restricted the analyses to first births, the overall effect increased slightly (relative risk, 1.7; 95 percent confidence interval, 1.3 to 2.3) and the estimated relative risk of a defect similar to the mother's also increased (data not shown).

In summary, girls with birth defects have higher mortality through at least their first 15 years of life than girls without birth defects. Once they reach reproductive age, they are less likely than other women to have children. Among the infants born to the women with birth defects who do reproduce, there is an increased risk of the same birth defect, but no increased risk of another birth defect. The increase in birth defects among these children accounts for a negligible share of the birth defects in the next generation — approximately 5 per 1000.

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